

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

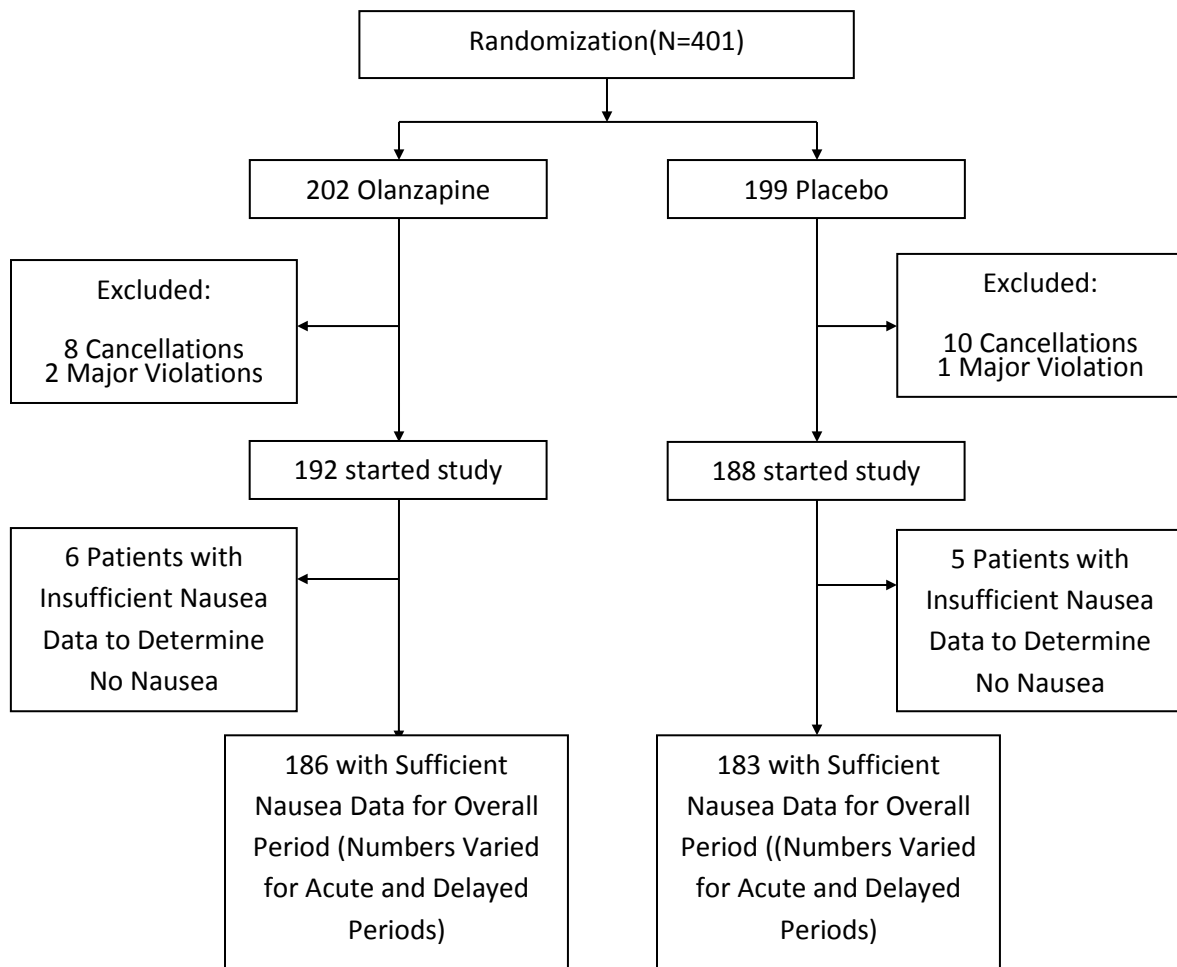
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Navari - Supplemental Statistical Material

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1. Figure S1 Consort diagram:



2. There are three major violations:

1 patient received wrong treatment; 1 pt received wrong treatment/arm ; 1 pts receive 20 mg Dexamethasone on day 1 per protocol patients should receive 12 mg .

3. The missing data nausea imputation: patients with missing data in Olanzapine arm were imputed as having Nausea, patients with missing data in Placebo arm were imputed as having no nausea. The data were not significant for overall period anymore.

Table S1 Primary Endpoint Summary Worst Cases					
	Olanzapine (N=192)	Placebo (N=188)	Total (N=380)	p value	Adjusted p value
Acute Nausea				<0.0001 ¹	0.0779
No Nausea	135 (70.3%)	89 (47.3%)	224 (58.9%)		
Had Nausea	57 (29.7%)	99 (52.7%)	156 (41.1%)		
Delayed Nausea				0.0572 ¹	0.0779
No Nausea	75 (39.1%)	56 (29.8%)	131 (34.5%)		
Had Nausea	117 (60.9%)	132 (70.2%)	249 (65.5%)		
Overall Nausea				0.0779 ¹	0.0779
No Nausea	66 (34.4%)	49 (26.1%)	115 (30.3%)		
Had Nausea	126 (65.6%)	139 (73.9%)	265 (69.7%)		
(report generated on 04FEB2016)					
¹ Chi-Square					

4. Table S2 Patients with acute nausea

	Olanzapine (N=48)	Placebo (N=99)	Total (N=147)	p value
Delayed Nausea				0.0375 ¹
Missing	1	1	2	
No Nausea	8 (17.0%)	6 (6.1%)	14 (9.7%)	
Had Nausea	39 (83.0%)	92 (93.9%)	131 (90.3%)	
¹ Chi-Square				

Table S3 Patients w/o acute nausea

	Olanzapine (N=135)	Placebo (N=82)	Total (N=217)	p value
Delayed Nausea				0.8277 ¹
Missing	7	4	11	
No Nausea	66 (51.6%)	39 (50.0%)	105 (51.0%)	
Had Nausea	62 (48.4%)	39 (50.0%)	101 (49.0%)	
¹ Chi-Square				

In addition, delayed nausea was compared between treatment arms after controlling for the presence of acute nausea. The odds of patients having delayed nausea is 9.18 times higher for patients with acute nausea than those who did not experience acute nausea. After adjusting for acute nausea, there was no significant drug effect on delayed nausea (p=0.2501)

Table S4 Odds Ratio Estimates

	Odds ratio	95% CI	P value
Nausea_acute(had nausea vs. no nausea)	9.182	(4.871 14.311)	<0.0001
Arm (Olanzapine to Placebo)	0.742	(0.446 1.234)	0.2501

5. The number of patients experiencing no significant nausea in each arm during the acute and delayed study periods.(No significant nausea is defined <3)

Table S5 Significant Nausea between Arms					
	Olanzapine (N=192)	Placebo (N=188)	Total (N=380)	p value	Adjusted P value
Acute Nausea				0.0001 ¹	0.0007
Missing	9	7	16		
No Significant Nausea	159 (86.9%)	127 (70.2%)	286 (78.6%)		
Had Significant Nausea	24 (13.1%)	54 (29.8%)	78 (21.4%)		
Delayed Nausea				0.0009 ¹	0.0009
Missing	15	11	26		
No Significant Nausea	127 (71.8%)	97 (54.8%)	224 (63.3%)		
Had Significant Nausea	50 (28.2%)	80 (45.2%)	130 (36.7%)		
Overall Nausea				0.0007 ¹	0.0007
Missing	15	10	25		
No Significant Nausea	118 (66.7%)	87 (48.9%)	205 (57.7%)		

Table S5 Significant Nausea between Arms					
	Olanzapine (N=192)	Placebo (N=188)	Total (N=380)	p value	Adjusted P value
Had Significant Nausea	59 (33.3%)	91 (51.1%)	150 (42.3%)		
¹ Chi-Square					

6 Missing data pattern (primary endpoint): blank stands for missing data, X stands for patients having data

Table S6

Day 2	Day 3	Day 4	Day 5	Day 6	N(total=380)
X	X	X	X	X	333
X	X	X	X		9
X	X	X			6
X	X	X		X	5
X	X				1
X	X		X	X	5
X		X	X	X	3
X					2
	X	X	X	X	2
	X				1
			X	X	1
				X	1
					11

7. The primary endpoint analysis for patient without missing data(N=333)

Table S7 Primary Endpoint Summary Complete Cases					
	Olanzapine (N=166)	Placebo (N=167)	Total (N=333)	p value	Adjusted P value
Acute Nausea				<0.0001 ¹	0.0013
No Nausea	121 (72.9%)	74 (44.3%)	195 (58.6%)		
Had Nausea	45 (27.1%)	93 (55.7%)	138 (41.4%)		
Delayed Nausea				0.0008 ¹	0.0013
No Nausea	74 (44.6%)	45 (26.9%)	119 (35.7%)		
Had Nausea	92 (55.4%)	122 (73.1%)	214 (64.3%)		
Overall Nausea				0.0013 ¹	0.0013
No Nausea	66 (39.8%)	39 (23.4%)	105 (31.5%)		
Had Nausea	100 (60.2%)	128 (76.6%)	228 (68.5%)		
¹ Chi-Square					

8 . The number of patients having incomplete data but at least some data (N=36) experiencing nausea at least once.

18 of the 36 patients experienced Nausea at least once (9 pts from each arm)

9. Missing data imputation (11 patients with no nausea at all were included, 401 patients in total)

Table S8 Primary Endpoint Summary(missing data were imputed as patients having nausea)					
	Olanzapine (N=202)	Placebo (N=199)	Total (N=401)	p value	Adjusted P value
Nausea Acute				<0.0001 ¹	0.0029
No Nausea	135 (66.8%)	82 (41.2%)	217 (54.1%)		
Had Nausea	67 (33.2%)	117 (58.8%)	184 (45.9%)		
Nausea Delayed				0.0015 ¹	0.0029
No Nausea	75 (37.1%)	45 (22.6%)	120 (29.9%)		
Had Nausea	127 (62.9%)	154 (77.4%)	281 (70.1%)		
Nausea Overall				0.0029 ¹	0.0029
No Nausea	66 (32.7%)	39 (19.6%)	105 (26.2%)		
Had Nausea	136 (67.3%)	160 (80.4%)	296 (73.8%)		
¹ Chi-Square					

Table S9 Primary Endpoint Summary(missing data were imputed as patients having no nausea)					
	Olanzapine (N=202)	Placebo (N=199)	Total (N=401)	p value	Adjusted P value
Nausea Acute				<0.0001 ¹	0.0021
No Nausea	154 (76.2%)	100 (50.3%)	254 (63.3%)		
Had Nausea	48 (23.8%)	99 (49.7%)	147 (36.7%)		
Nausea Delayed				0.0013 ¹	0.0021
No Nausea	100 (49.5%)	67 (33.7%)	167 (41.6%)		
Had Nausea	102 (50.5%)	132 (66.3%)	234 (58.4%)		
Nausea Overall				0.0021 ¹	0.0021
No Nausea	91 (45.0%)	60 (30.2%)	151 (37.7%)		
Had Nausea	111 (55.0%)	139 (69.8%)	250 (62.3%)		
¹ Chi-Square					

10. Multiple imputation has been performed to supplement missing acute, delayed or overall nausea, then logistic regression models was used to analyze imputed data sets and save parameter estimates and corresponding covariate matrices and then combine them to generate statistical inference.

Table S10 Odds Ratio Estimates

	Odds ratio (Olanzapine vs. Placebo)	95% CI	P value	Adjusted P value
Acute	3.493	(2.259 5.402)	<0.0001	0.0006
Delayed	2.390	(1.546 3.695)	<0.0001	0.0006
Overall	2.231	(1.408 3.535)	0.0006	0.0006

At the final analysis, the odds of patients who had no nausea (the primary endpoint) was significantly greater for the olanzapine regimen compared to the placebo regimen for the acute (OR=3.493, p=0.0006), the delayed (OR=2.390, p=0.0006), and the overall (2.231, p=0.0006) periods (Table 2A), and the primary results was confirmed to remain statistically significant as we did in the manuscript.

11.

Table 3 (Table S11) Sedation scores¹ on Day 2 post-chemotherapy

Sedation Scores	Olanzapine (N=192)	Placebo (N=188)
0	104 (57.5%)	118 (65.2%)
1	11 (6.1%)	18 (9.9%)
2	3 (1.7%)	12 (6.6%)
3	14 (7.7%)	7 (3.9%)
4	4 (2.2%)	7 (3.9%)
5	8 (4.4%)	7 (3.9%)
6	7 (3.9%)	4 (2.2%)
7	5 (2.8%)	2 (1.1%)
8	15 (8.3%)	3 (1.7%)
9	4 (2.2%)	2 (1.1%)
10	6 (3.3%)	1 (0.6%)
Missing	11	7

¹ As determined by patients completing an 11-point (0-10) numerical analogue scales daily, regarding whether they had any 'undesired sedation'.